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IN THE UNITED STATES PATENT & TRADEMARK OFFICE

IN RE APPLICATION OF	:
ANGELO GUGLIELMOTTI, ET AL.	: EXAMINER: RAMACHANDRAN, U.
SERIAL NO: 10/560,836	:
FILED: MARCH 30, 2006	: GROUP ART UNIT: 1617
FOR: USE OF 2H-[1,3]-OXAZINO [3, 2-A] INDOLE DERIVATIVES FOR THE TREATMENT OF NEUROPATHIC PAIN	:

APPEAL BRIEF

COMMISSIONER FOR PATENTS

ALEXANDRIA, VIRGINIA 22313

SIR:

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(i) Real Party in Interest

Aziende Chimiche Riunite Angelini Francesco A.C.R.A.F. S.p.A. is the real party in interest.

(ii) Related Appeals or Interferences

The Appellants are unaware of any related appeals or interferences that would directly affect, be directly affected by, or have a bearing on the Board's decision in this appeal.

(iii) Status of the Claims

Claims 6-12 and 14-23 are on Appeal. Claim 6 is the only independent claim on Appeal.

Claims 1-5, 13 and 24 have been cancelled.

The Claims Appendix below provides a clean copy of the claims on appeal entered by the Amendment filed along with this Appeal Brief.

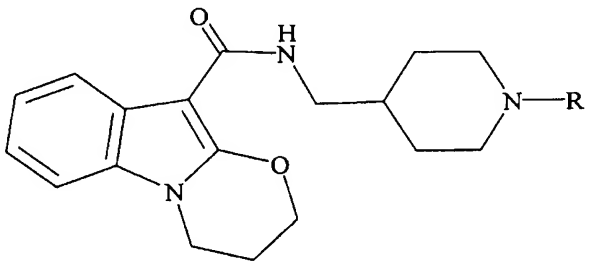
(iv) Status of the Amendment

The Amendment filed herewith (cancelling claims 13 and 24) will be entered for purposes of Appeal based on a telephonic conversation with the Examiner on May 12, 2008.

(v) Summary of the Claimed Subject Matter

Claim 6 is directed to a method for treating **neuropathic pain**--an abnormal type of pain (unlike nociceptive pain perceived via non-damage nervous tissue) which results from nerve damage by administering a compound of formula I. Descriptive support for claim 6 is found in original claim 1 which describes both formula I and the treatment of neuropathic pain.

Claim 6: A method for the treatment of neuropathic pain comprising: administering to a subject in need thereof a compound of formula I:



wherein

R is H, a linear or branched alkyl chain having from 1 to 12 carbon atoms, or an arylalkyl group;

or a pharmaceutically acceptable acid-addition salt thereof.

Some Background on Neuropathic Pain

This section defines some of the key terms such as **neuropathic pain**, **allodynia** and **hyperalgesia** important for understanding the issues in the obviousness rejections. As will be apparent, the obviousness rejections on Appeal are each based on an assumption that drugs that treat certain symptoms of *nociceptive pain* (e.g., allodynia or hyperalgesia) will also treat **neuropathic pain**. Based on this assumption, the Examiner alleges that functional classes of drugs (e.g., 5-HT4 receptor antagonists) which treat *nociceptive pain* accompanied by the symptoms such

as **allodynia**, would also be expected to treat **neuropathic pain**. The conflation of treatment of **neuropathic pain** with treatment of *nociceptive pain* is erroneous for the following reasons.

Neuropathic ("neuro-" nerve, "-pathic" to suffer) **pain** is **NOT** ordinary pain. Unlike normal *nociceptive* pain which is perceived via normal, healthy neural tissue, **neuropathic** pain is associated with damage to the neural tissue itself. This abnormal type of pain is usually perceived as a steady burning and/or "pins and needles" and/or "electric shock" sensations and/or tickling.

> "With neuropathic pain, the nerve fibers themselves may be damaged, dysfunctional or injured. These damaged nerve fibers send incorrect signals to other pain centers. The impact of nerve fiber injury includes a change in nerve function both at the site of injury and areas around the injury" (attached in Evidence Appendix) and at: http://www.medicinenet.com/neuropathic_pain/article.htm.

The IASP (International Association for the Study of Pain) describes neuropathic pain as "a pain initiated or caused by a primary lesion or dysfunction in the nervous system". Other medical references also show that **neuropathic** pain is recognized as a distinct type of pain and has unique characteristics distinguishing it from nociceptive pain; see Dorland's Illustrated Medical Dictionary http://www.mercksource.com/pp/us/cns/cns_hl_dorlands.jspzQzpgzEzzSzppdocszSzuszSzcommonzSzdorlandszSzdorlandzSzdmd_p_02zPzhtm (attached in Evidence Appendix). For example, Neuropathic pain is distinguishable from *nociceptive* abdominal pain, such as that induced in the Smith, et al. animal model of intestinal allodynia, see: http://www.medicinenet.com/abdominal_pain/article.htm (printout attached in Evidence Appendix).

Neuropathic pain is very difficult to treat and is recognized in the art as not being amenable to the same treatments used to treat normal *nociceptive pain*.

"Unfortunately, neuropathic pain often responds poorly to standard pain treatments and occasionally may get worse instead of better over time. For some people, it can lead to serious disability", http://www.medicinenet.com/neuropathic_pain/article.htm (see Evidence Appendix).

Allodynia is a pain symptom and cannot be equated and is not associated strictly with either **neuropathic** pain or *nociceptive* pain. The IASP describes allodynia as denoting "a pain due to a stimulus which does not normally provoke pain". The term allodynia was originally introduced to separate from hyperalgesia and hyperesthesia, the conditions seen in patients with lesions of the nervous system where touch, light pressure, or moderate cold or warmth evoke pain when applied to apparently normal skin. Allo means "other' in Greek and is a common prefix for medical conditions that diverge from the expected. Odynia is derived from the Greek word "odune" or "odyne," which is used in "pleurodynia" and "coccydynia" and is similar in meaning to the root from which we derive words with -algia or -algesia in them. Allodynia was suggested following discussions with Professor Paul Potter of the Department of the History of Medicine and Science at The University of Western Ontario. The words "to normal skin" were used in the original definition but later were omitted in order to remove any suggestion that allodynia applied only to referred pain. Originally, the pain-provoking stimulus was described as 'non-noxious'. However, a stimulus may be noxious at some times and not at others, for example, with intact skin and sunburned skin, and also, the boundaries of noxious stimulation may be hard to delimit. Since the Committee aimed at providing terms for clinical use, it did not wish to define them by reference to the specific physical characteristics of the stimulation, e.g., pressure in kilopascals per square centimeter. Moreover, even in intact skin there is little evidence one way or the other that a strong

painful pinch to a normal person does or does not damage tissue. Accordingly, it was considered to be preferable to define allodynia in terms of the response to clinical stimuli and to point out that the normal response to the stimulus could almost always be tested elsewhere in the body, usually in a corresponding part. Allodynia also describes conditions which may give rise to sensitization of the skin, e.g. sunburn inflammation, trauma. It is important to recognize that **allodynia** involves a change in the quality of a sensation, whether tactile, thermal, or of any other sort. The original modality is normally non-painful, but the response is painful. There is thus a loss of specificity of a sensory modality.

There are different types of allodynia. The cold allodynia of Jorum, et al., a type of thermal allodynia associated with neuropathic pain, is symptomatically distinguishable from the mechanical or tactile allodynia exemplified by the animal model of Smith, et al., see http://en.wikipedia.org/wiki/Allodynia (attached in Evidence Appendix). For example, pain induced by normally mild skin temperatures characterize cold allodynia, while light pressure of other tactile stimuli induce pain that characterizes mechanical allodynia. Thus, different types of nociception characterize thermal and mechanical allodynia.

By contrast to allodynia, **hyperalgesia** (*q.v.*) represents an augmented response in a specific mode, viz., pain. With other cutaneous modalities, hyperesthesia is the term which corresponds to hyperalgesia, and as with hyperalgesia, the quality is not altered. In allodynia the stimulus mode and the response mode differ, unlike the situation with hyperalgesia. This distinction should not be confused by the fact that allodynia and hyperalgesia can be plotted with overlap along the same continuum of physical intensity in certain circumstances, for example, with pressure or temperature.

Hyperalgesia denotes an increased response to a stimulus which is normally painful. Hyperalgesia reflects increased pain on suprathreshold stimulation. For pain evoked by stimuli that usually are not painful, the term allodynia is preferred, while hyperalgesia is more appropriately used for cases with an increased response at a normal threshold, or at an increased threshold, e.g., in patients with neuropathy. It should also be recognized that with allodynia the stimulus and the response are in different modes, whereas with hyperalgesia they are in the same mode. Current evidence suggests that hyperalgesia is a consequence of perturbation of the nociceptive system with peripheral or central sensitization, or both, but it is important to distinguish between the clinical phenomena, which this definition emphasizes, and the interpretation, which may well change as knowledge advances.

(vi) Grounds of Rejection to be Reviewed on Appeal

A. Whether Claims 6-12 and 14-17 are obvious under 35 U.S.C. 103(a) over Gaster et al., EP 0630376[1], in view of Smith et al., Neurosci. Lett. 271:61 and Jorum et al., Pain 101:229.

B. Whether Claims 6-12 and 14-17 are obvious under 35 U.S.C. 103(a) over Gaster et al., EP 0630736, in further in view of Burnstein et al., Brain 123:1703 and Jorum et al., Pain 101:229.

C. Whether Claims 18-20 are obvious under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630376[2], in view of Smith et al., Neurosci. Lett. 271:61 and Jorum et al., Pain 101:229, and further in view of Wickenden, U.S. Patent No. 6,326,385.

D. Whether Claims 20-23 are obvious under 35 U.S.C. 103(a) over Gaster et al., EP 0630376[3], in view of Smith et al., Neurosci. Lett. 271:61 and Jorum et al., Pain 101:229, and further in view of Omoigui, et al., U.S. 2004/0038874.

[1] Cited as EP 0630736 in the Official Action.
[2] Cited as EP 0630736 in the Official Action.
[3] Cited as EP 0630736 in the Official Action.

(vii) Argument(s)

Issue A: Rejection—35 U.S.C. §103(a)

Claims 6-12 and 14-17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630376[4], in view of Smith et al., Neurosci. Lett. 271:61 and Jorum et al., Pain 101:229. These documents do not render the claimed invention obvious because they do not suggest or provide a reasonable expectation of success for treating **neuropathic pain** (associated with damaged nerve tissue) using a compound of formula (I).

Gaster was cited as disclosing compounds of formula I for treating irritable bowel syndrome, migraine, etc. Gaster does not disclose treatment of **neuropathic pain** as admitted on page 4, lines 1-2 of the Official Action of September 12, 2007..

Smith is cited as disclosing that SB 207266—a compound chemically distinct from formula I (but which is disclosed as a functional 5-HT4 receptor antagonist) potentiates inhibition of intestinal allodynia. Smith does not disclose treatment of neuropathic pain or use of a compound of formula I and the Official Action (page 4, line 5) admits that it does not teach that **neuropathic pain** and (intestinal) allodynia are the same.

Jorum is relied upon for teaching that the symptoms of allodynia and hyperalgesia are "frequent clinical findings in patients with neuropathic pain", see page 4, lines 6-7 of the Official Action. However, Jorum does not teach that intestinal allodynia of Smith is the same as the allodynia associated with neuropathic pain, is silent with respect to compounds of formula I and is non-analogous art because it involves the use of μ opioid agonists distinct from formula I of the invention and distinct from SB207266 of Smith.

[4] Cited as EP 0630736 in the Official Action.

The teachings of each of the cited references are summarized below:

Invention	Gaster, et al.	Smith, et al.	Jorum
Neuropathic Pain, resulting from "damage to the nervous system", Woolf, et al., Lancet 353:1959.	Pain associated with [0050] irritable bowel syndrome, reflux, dyspepsia, arrhythmia, stroke, anxiety, migraine.	Experimental Intestinal Allodynia: caused by intra-anal insertion of balloon and 5-HT dosing. Inflation of balloon to measure distension pressure in intestines as measure of allodynia.	Cold allodynia and hyperalgesia are frequent clinical findings in patients with neuropathic pain.
formula I--Yes	formula I--Yes.	formula I--No	formula I--No
	Compounds of formula I are 5-HT-4 receptor antagonists	5-HT4 receptor antagonist SB 207266	Alfentanil is μ-opioid agonist, not a 5-HT4 receptor antagonist
	No suggestion to treat neuropathic pain.	No suggestion to treat neuropathic pain.	No suggestion that Formula I would treat neuropathic pain.
		Tactile or mechanical allodynia not associated with neuropathic pain.	Thermal allodynia

There is no suggestion in the prior art as a whole to administer a compound of formula I to treat **neuropathic pain**. **Neuropathic pain** is a specific type of pain associated with nerve damage that is distinct from nociceptive pain (pain sensed by undamaged nervous tissue). **Neuropathic pain**, as explained above is distinct from nociceptive pain associated with other diseases and denotes a pain initiated or caused by a primary lesion or dysfunction in the nervous system.

Gaster [0050] only describes treatment of irritable bowel syndrome, gastro-oesophagal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or

migraine with compounds of formula (I). It not disclose or suggest use of these compounds for treating **neuropathic pain** associated with damaged nerves.

Smith and Jorum do not disclose the compounds of formula (I), provide no suggestion or reasonable expectation of success for using compounds of formula (I) to treat **neuropathic pain**.

This rejection conflates the thermal allodynia of Jorum with the mechanical allodynia of Smith. The Examiner's reasoning is that Smith's 5-HT4 receptor antagonist SB 207266 (which is not a compound of formula I) ameliorates intestinal allodynia, therefore the whole class of 5-HT4 receptor antagonist compounds would also have been expected to ameliorate thermal allodynia of Jorum and thus treat **neuropathic pain**. The Appellants respectfully traverse this reasoning because:

(i) the prior art does not disclose or suggest that thermal allodynia, such as that disclosed by Jorum, can be treated with the **class** of 5-HT4 receptor antagonists of which the Smith compound SB 207266 is one example. Smith does not say this and Jorum in fact uses a completely different class of drug—a **μ-opioid antagonist** to treat thermal allodynia. The Examiner is alleging that 5-HT receptor antagonists generally ameliorate neuropathic pain, but there is no support in the prior art for this allegation.

Moreover, the thermal allodynia (Jorum) and mechanical allodynia (Smith) are distinct from one another and involve different types of nociception. Thus, an ability of SB 207266 of Smith to treat mechanical allodynia does not predict its capacity to treat thermal allodynia of Jorum.

Assuming *arguendo* that the prior art disclosed that both thermal and mechanical allodynia could be treated with the functional class of 5-HT4 receptor antagonists, the cited references still would have provided no suggestion to treat

neuropathic pain caused by damage nerve tissue using a 5-HT4 antagonist. Smith does not indicate that the functional class of 5-HT4 receptor antagonists generally exert anti-allodynic effects, though this is assumed by the Examiner's argument on page 4 of the Official Action. Smith teaches that:

> 5-HT4 receptor antagonism potentiates inhibition of intestinal allodynia by 5-HT3 receptor antagonism.

It does not disclose that a 5-HT4 receptor antagonist would have any effect on intestinal allodynia in the absence of a 5-HT3 receptor antagonist. In fact, page 61, first col. specifically states that:

> 5-HT4 receptor antagonism does **not** affect normal pseudoeffective or visceromotor reflexes evoked by noxious levels of colo-rectal distension in anesthetized or conscious rats (emphasis added).

Smith only indicates that 5-HT4 receptor antagonists **potentiate** inhibition of intestinal allodynia by a **5-HT3 receptor antagonist** (see summary, line 3, as well as page 61, right column, line 7 to 9; and Fig. 1 on page 62) and that "$5HT_4$ receptor activation enhances the ability of $5HT_3$ receptor activation to induce intestinal allodynia" (see summary, last two lines). Smith is silent about the effects of administering a 5-HT4 antagonist. Thus, the Examiner has not shown the prior art suggests a nexus between the administration of any 5-HT4 receptor antagonist *per se* (or a compound of formula I) and treatment of allodynia of any type.

Moreover, the Official Action provides no evidence that a compound of formula (I) is **both** a 5-HT3 and 5-HT4 receptor antagonist as taught by Smith. Significantly, the test used by Smith does not involve allodynia associated with damaged nerve tissue or any primary lesion or dysfunction in the nervous system. Smith teaches an animal model for nociceptive allodynia, not for neuropathic pain. Therefore, the experimental data disclosed by Smith can not be correlated with **neuropathic pain** in any way. Indeed, a pain cannot be defined as neuropathic in the

absence of a primary lesion or dysfunction in the nervous system (see the definition above) and the test used by Smith did not involve any primary lesion or dysfunction in the nervous system (nerve damage). Therefore, the experimental data disclosed by Smith cannot be correlated with **neuropathic pain** in any way.

(iii) The Examiner has presumed that structurally distinct compounds that exhibit some degree of antagonism on 5-HT4 receptors as taught by Smith would have similar effects on thermal allodynia associated with neuropathic pain as described by Jorum. However, the Examiner has not explained why structurally different compounds would have been expected to exhibit the same effects. The compound of formula I is structurally distinct SB-207266 compound of Smith. Smith provides no evidence that other structurally distinct 5HT4 antagonists (e.g., the compound of formula I) would have any effect on intestinal allodynia or on thermal allodynia, and no suggestion at all that that a compound of formula (I) would treat **neuropathic pain**. The Examiner has demonstrated no nexus between antagonism of 5-HT4 receptors and treatment of neuropathic pain or even thermal allodynia associated with neuropathic pain.

Jorum does not remedy the deficiencies Gaster or Smith. Jorum discloses that Alfentanil significantly reduced cold allodynia (see summary, line 10). However, this reference is silent about the action of Alfentanil on neuropathic pain. Moreover, Alfentanil is μ-opioid agonist, not a 5-HT_4 receptor antagonist and not a compound of formula I. Thus, Jorum is **non-analogous** art because it discloses a different class of drugs, does not disclose compounds of formula I, and discloses nothing about the effects of drugs on neuropathic pain or thermal allodynia associated with neuropathic pain.

While the Examiner is correct stating that Jorum teaches that allodynia and hyperalgesia are frequent clinical findings in patient with neuropathic pain, the Examiner is wrong by speculating that inhibiting allodynia in patients would provide a method of treating a **neuropathic pain**. Particularly, Jorum is completely silent about the action of Alfentanil on neuoropathic pain. There is no basis at all in Smith to infer that SB 207266 shows an anti-allodynic activity in the absence of a 5-HT_3 receptor antagonist, and no basis in Jorum to infer that inhibiting allodynia in patients would provide a method of treating a neuropathic pain.

On the other hand, the inventors show in Figs. 1 and 2, the efficacy of the compound of formula (I) to treat **neuropathic pain** in two different models: pain threshold after sciatic nerve ligature and by the effects on pain threshold in diabetic neuropathy. As shown, control animals that did not receive the compound of formula (I) have significantly lower pain thresholds than treated animals and a dose-response relationship was demonstrated.

Therefore, since the prior art does not disclose, suggest or provide a reasonable expectation of success for the invention, the Appellants respectfully request that this rejection be reversed.

Issue B: Rejection—35 U.S.C. §103(a)

Claims 6-12 and 14-17 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630736, and further in view of Burnstein et al., Brain 123:1703 and Jorum et al., Pain 101:229. Gaster and Jorum have been addressed above. Neither discloses or suggests using a compound of formula (I) to treat neuropathic pain. Only Gaster describes a compound of formula (I); Jorum is

directed to treatments using a different class of drugs: μ-opioid agonists, not 5-HT_4 receptor antagonists.

Burnstein describe the development of cutaneous allodynia during a migraine attack. However, nothing in this reference teaches or suggests that a class of drugs capable of treating cutaneous allodynia will successfully treat migraine, or more importantly, neuropathic pain.

Significantly, there is no link whatsoever between migraine (which is thought to arise from chemical activation of sensory nerves that supply intracranial blood vessels and meninges, see the first six lines of Burnstein) and **neuropathic pain** which is caused by a primary lesion or dysfunction in the nervous system. Thus, there cannot be any reasonable expectation of success for treating **neuropathic pain** using a compound that treats cutaneous allodynia or migraine not associated with nerve damage.

Moreover, to link migraine to neuropathic pain via allodynia, Burstein should teach that a fully developed migraine attack benefits from a possible drug capable of treating cutaneous allodynia. In contrast, Bernstein is completely silent about the effects on migraine of drugs capable of treating cutaneous allodynia.

In turn, Jorum does not establish a link between the treatment of allodynia and the treatment of neuropathic pain. Indeed, Jorum et al. teaches that Alfentanil is useful to treat allodynia only. However, it is completely silent about the action of Alfentanil on the neuropathic pain.

Thus, there is no suggestion or reasonable expectation of success in Gaster, Burstein or Jorum that inhibiting allodynia would provide a method of treating a **neuropathic pain**. Accordingly, the Appellants respectfully request that this

rejection be reversed as none of the cited prior art suggests or provide a reasonable expectation of success for use of a compound of formula I to treat **neuropathic pain.**

Issue C: Rejection—35 U.S.C. §103(a)

Claims 18-20 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630376[5], in view of Smith et al., Neurosci. Lett. 271:61 and Jorum et al., Pain 101:229, and further in view of Wickenden, U.S. Patent No. 6,326,385. The primary references have been addressed above: none suggest using a compound of formula (I) to treat neuropathic pain.

Wickenden was cited as showing that neuropathic pain is associated with injury to the central or peripheral nervous system. However, Wickenden does not disclose a compound of formula I or provide a reasonable expectation of success for treatment of neuropathic pain with such a compound.

This argument is also based on the Examiner's assumption that a 5-HT4 receptor antagonist will treat the symptom of allodynia associated with any disease--including treating the thermal allodynia described by Jorum. However, the prior art does not suggest that a 5-HT4 receptor antagonist will have such an effect or that such an antagonist is there is generally useful for treating neuropathic pain, or, specifically, that a compound of formula (I) should be used for this purpose. Therefore, this rejection should also be reversed.

Issue D: Rejection—35 U.S.C. §103(a)

[5] Cited as EP 0630736 in the Official Action.

Claims 20-23 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Gaster et al., EP 0630376[6], in view of Smith et al., Neurosci. Lett. 271:61 and Jorum et al., Pain 101:229, and further in view of Omoigui, et al., U.S. 2004/0038874. The primary references have been addressed above--none suggest using a compound of formula (I) to treat neuropathic pain.

Omoigui was cited as showing that neuropathic pain is associated with inflammation. This document describes "treating persistent pain disorders by inhibiting the biochemical mediators of **inflammation** (emphasis added)", abstract. Paragraph [0051] refers to release of Substance P from injured nerves as an "important early event in the induction of neuropathic pain". However, these teachings are merely hypothetical and theoretical as clear from paragraph [0001]:

> The invention relates to a method of treatment of persistent pain by application of Sota Omoigui's Law, which states: The origin of all pain is inflammation and the inflammatory response. Irrespective of the type of pain whether it is acute pain as in a sprain, sports injury of Euro charge jellyfish sting or whether it is chronic pain as in arthritis, migraine pain, back or neck pain from herniated disks, REDCAPS pain, migraine, Fibromyalgia, Interstitial cystitis, Neuropathic pain, Post-stroke pain, etc., the underlying basis the inflammation and the inflammatory response. Irrespective of the characteristic of the pain, whether it is sharp, dull, aching, burning, stabbing, numbing or tingling, all pain arise from inflammation and the inflammatory process.

According to the author, the origin of all kinds of pain are the biochemical mediators of inflammation and the inflammatory response, so that, to treat pain, it is sufficient to block these mediators and block the signals they send up through the nerve cells. Unfortunately, most of this patent publication is based on a literature reference published in "medical hypothesis", a journal of the Elsevier group which has the purpose "to publish interesting theoretical papers" and to "consider radical,

[6] Cited as EP 0630736 in the Official Action.

speculative and non-mainstream scientific ideas", see Enclosure 1 attached in Evidence Appendix. The reference is "The biochemical origin of pain--Proposing a new law of pain: The origin of all pain is inflammation and the inflammatory response. Part 1 of 2--A unifying law of pain", Medical Hypotheses, Vol. 69(1), pages-82 (see Enclosure 2 attached in the Evidence Appendix). Thus, this document fails to provide a reasonable expectation of success for treating neuropathic pain with a compound of formula I.

The rest of Omoigui's patent publication is based on a literature reference E-published on August 27, 2007 in the very same journal "The biochemical origin of pain: The origin of all pain is inflammation and the inflammatory response. Part 2 of 3--Inflammatory profile of pain syndromes, see Enclosure 3 attached in the Evidence Appendix. As explained above, the content of these literature references is highly speculative and theoretical, lacks confirmatory scientific support in the scientific and academic world, and provides no reasonable expectation of success for treating neuropathic pain using a compound of formula I.

Moreover, a plain reading of Omoigui [0051] and [0068-0069] does not reveal a common mechanism linked to Substance P between the naturopathic pain and pain associated with migraine. Paragraph [0051] simply states that the induction of neuropathic pain is a chain of events which comprises the release of substance P from injured nerves which then increases local Tumor Necrosis Factor α (TNF-α) production, which then together attract and activate immune monocytes and macrophages. The mechanism is then much more complex than that considered by the Examiner, and involves another product (TNF-α) and the activation of specific cellular types.

Paragraph [0051] ends stating that inhibition of macrophage recruitment to the nerve injury site, or pharmacological interference with TNF-α production has been shown to reduce both the neuropathological and behavioral manifestations of neuropathic pain states. There is no mention of treatment of neuropathic pain states with any substance interfering with Substance P.

Paragraphs [0068-0069] deal with a completely different theoretical mechanism. Here, and in particular in the last 4 lines of page 7 and in the last 18 lines of page 8, substance P is only associated with calcitonin gene-related peptides (CGRP) and it is said that this latter molecule is responsive for vasodilatation (a well known cause of migraine) and an increase in dural arterial flow, but not substance P. Substance P is said to have a role in mediating plasma leakage from small veins in the *dura mater* (which is not known to be related to migraine).

Even if both these sections of Omoigui deal with Substance P, the mechanisms involved are substantially different and involve different tissues, different biochemical products, and different cellular types. It cannot simply be concluded that treating with a substance interfering with substance P would result in a treatment of both neuropathic pain and migraine. There is no reasonable expectation of such in Omoigui.

On the contrary, the scientific literature shows that receptor antagonists for substance P are not effective for analgesia, see Hill, TIBS 21, "NK1 (substance P) receptor antagonist--why are they not analgesic in humans?", see Enclosure 4 attached in Evidence Appendix. Accordingly, the teachings of Omoigui are theoretical and cannot provide any reasonable expectation of success for the invention. As discussed above, these teachings are hypothetical and not supported by the scientific literature. Accordingly, this rejection should be reversed.

RELIEF REQUESTED

The Appellants respectfully request REVERSAL of the remaining grounds of rejection.

Respectfully submitted,

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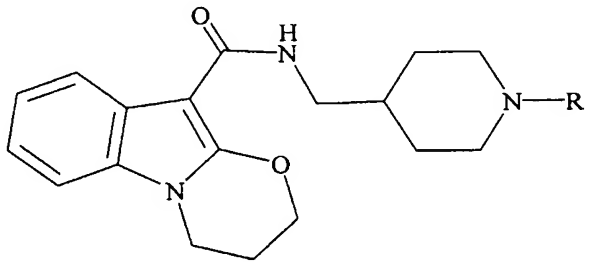
(viii) Claims Appendix

Claims 1-5 (Cancelled)

Claim 6 (Previously Presented): A method for the treatment of neuropathic pain comprising:

administering to a subject in need thereof a compound of formula I:



wherein

R is H, a linear or branched alkyl chain having from 1 to 12 carbon atoms, or an arylalkyl group;

or a pharmaceutically acceptable acid-addition salt thereof.

Claim 7 (Previously Presented): The method of claim 6, wherein R is H.

Claim 8 (Previously Presented): The method of claim 6, wherein R is a linear or branched alkyl chain having 1 to 12 carbon atoms.

Claim 9 (Previously Presented): The method according to claim 6, wherein R is an n-butyl group.

Claim 10 (Previously Presented): The method of claim 6, wherein R is an arylalkyl group.

Claim 11 (Previously Presented): The method according to claim 6, wherein R is an arylalkyl group where the aryl moiety is phenyl.

Claim 12 (Previously Presented): The method of claim 6, wherein R is an arylalkyl group where the aryl moiety is naphthyl.

Claim 13 (Cancelled)

Claim 14 (Previously Presented): The method of claim 6, wherein R is an arylalkyl group where the alkyl moiety has from 1 to 4 carbon atoms.

Claim 15 (Previously Presented): The method of claim 6, comprising administering a pharmaceutical composition comprising said compound of formula (I), or acid-addition salt thereof, and at least one pharmaceutically acceptable inert ingredient.

Claim 16 (Previously Presented): The method of claim 6, wherein said subject has allodynia.

Claim 17 (Previously Presented): The method of claim 6, wherein said subject has hyperalgesia.

Claim 18 (Previously Presented): The method of claim 6, wherein said subject has neuropathic pain associated with diabetes.

Claim 19 (Previously Presented): The method of claim 6, wherein said subject has neuropathic pain associated with cancer.

Claim 20 (Previously Presented): The method of claim 6, wherein said subject has neuropathic pain associated with immunodeficiency, trauma, ischaemia, multiple sclerosis, sciatic neuralgia, trigeminal neuralgia or a post-herpetic syndrome.

Claim 21 (Previously Presented): The method of claim 6, wherein said compound, or acid-addition salt thereof, is administered orally.

Claim 22 (Previously Presented): The method of claim 6, wherein said compound, or acid-addition salt thereof, is administered by injection or aerosol.

Claim 23 (Previously Presented): The method of claim 6, wherein said compound, or acid-addition salt thereof, is administered transdermally or rectally.

Claim 24 (Cancelled)

(ix) Evidence Appendix

(see appended references)

(x) Related Proceedings Appendix

(none)